

Clean Set of Pending Claims

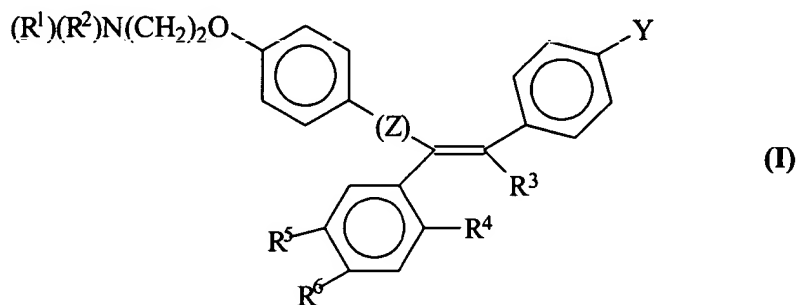
Title: Prevention and Treatment of Cardiovascular Pathologies with Tamoxifen Analogues

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158. (New) A therapeutic method comprising inhibiting non-aortal vascular smooth muscle cell proliferation associated with procedural vascular trauma comprising administering to a mammal, such as a human, subjected to said procedural vascular trauma an effective cytostatic antiproliferative amount of a compound of formula (I):



wherein Z is C=O or a covalent bond; Y is H or O(C₁-C₄)alkyl, R¹ and R² are individually (C₁-C₄)alkyl or together with N are a saturated heterocyclic group, R³ is ethyl or chloroethyl, R⁴ is H or together with R³ is -CH₂-CH₂- or -S-, R⁵ is I, OH, O(C₁-C₄)alkyl or H and R⁶ is I, O(C₁-C₄)alkyl or H; or a pharmaceutically acceptable salt thereof.

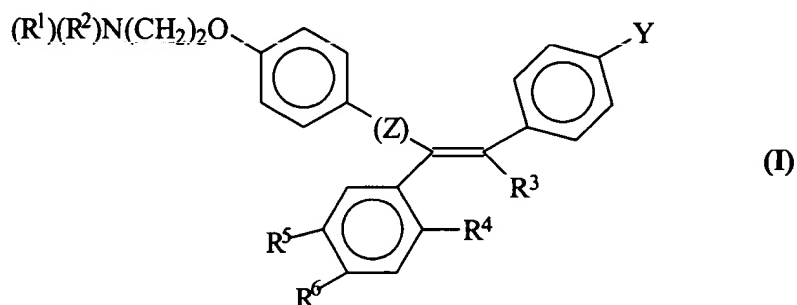
159. (New) The method of claim 158 wherein the compound of formula (I) is tamoxifen or a pharmaceutically acceptable salt thereof.
160. (New) The method of claim 158 wherein the compound of formula (I) is

idoxifene or a pharmaceutically acceptable salt thereof.

- 161. (New) The method of claim 158 wherein the compound of formula (I) is toremifene or a pharmaceutically acceptable salt thereof.
- 162. (New) The method of claim 158 wherein the administration is to a human patient.
- 163. (New) The method of claim 158 wherein the administration is before, during or after said procedure.
- 164. (New) The method of claim 158 wherein the administration is in a series of spaced doses.
- 165. (New) The method of claim 158 wherein the administration is parenteral.
- 166. (New) The method of claim 158 wherein the administration is oral.
- 167. (New) The method of claim 158 wherein the administration is systemic.
- 168. (New) The method of claim 158 wherein the compound of formula (I) is administered via a sustained release dosage form.
- 169. (New) The method of claim 158 wherein the administration is localized at the site of the vascular trauma.
- 170. (New) The method of claim 158 wherein the compound directly or indirectly increases the level of active TGF-beta.
- 171. (New) The method of claim 158 wherein the compound of formula (I) is

raloxifene, or a pharmaceutically acceptable salt thereof.

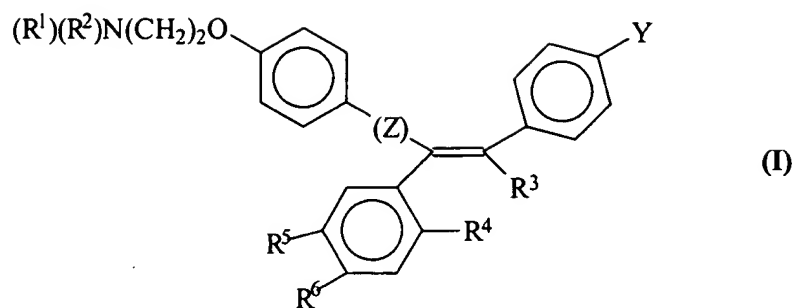
172. (New) The method of claim 158 wherein the compound of formula (I) is droloxifene, or a pharmaceutically acceptable salt thereof.
173. (New) A therapeutic method for preventing or treating a cardiovascular or vascular indication characterized by a decreased lumen diameter comprising administering to a mammal at risk of or afflicted with said cardiovascular or vascular indication, a cytostatic dose of a therapeutic agent, wherein the therapeutic agent is a compound of formula (I):



wherein Z is C=O or a covalent bond; Y is H or O(C₁-C₄)alkyl, R¹ and R² are individually (C₁-C₄)alkyl or together with N are a saturated heterocyclic group, R³ is ethyl or chloroethyl, R⁴ is H, R⁵ is I, O(C₁-C₄)alkyl or H and R⁶ is I, O(C₁-C₄)alkyl or H with the proviso that when R⁴, R⁵, and R⁶ are H, R³ is not ethyl; or a pharmaceutically acceptable salt thereof.

174. (New) The method of claim 173 wherein the cytostatic dose is effective to increase the level of TGF-beta so as to decrease lesion formation or development, inhibit lipid accumulation, increase plaque stability, maintain or increase vessel lumen diameter, or any combination thereof.

175. (New) The method of claim 173 wherein the compound of formula (I) is idoxifene, 4-iodotamoxifen, 3-iodotamoxifen, toremifene, or a pharmaceutically acceptable salt thereof.
176. (New) The method of claim 173 wherein the compound of formula (I) is idoxifene or a pharmaceutically acceptable salt thereof.
177. (New) The method of claim 173 wherein the compound of formula (I) is toremifene or a pharmaceutically acceptable salt thereof.
178. (New) The method of claim 173 wherein the administration is systemic.
179. (New) The method of claim 173 wherein the compound of formula (I) is administered via a sustained release dosage form.
180. (New) The method of claim 173 wherein the administration is localized at the site of the vascular trauma.
181. (New) The method of claim 173 wherein the compound directly or indirectly increases the level of active TGF-beta.
182. (New) A therapeutic method of increasing the level of TGF-beta in a mammal in need thereof, comprising administering an effective amount of a compound of formula (I):



wherein Z is C=O or a covalent bond; Y is H or O(C₁-C₄)alkyl, R¹ and R² are individually (C₁-C₄)alkyl or together with N are a saturated heterocyclic group, R³ is ethyl or chloroethyl, R⁴ is H or together with R³ is -CH₂-CH₂- or -S-, R⁵ is I, OH, O(C₁-C₄)alkyl or H and R⁶ is I, O(C₁-C₄)alkyl or H with the proviso that when R⁴, R⁵, and R⁶ are H, R³ is not ethyl; or a pharmaceutically acceptable salt thereof.

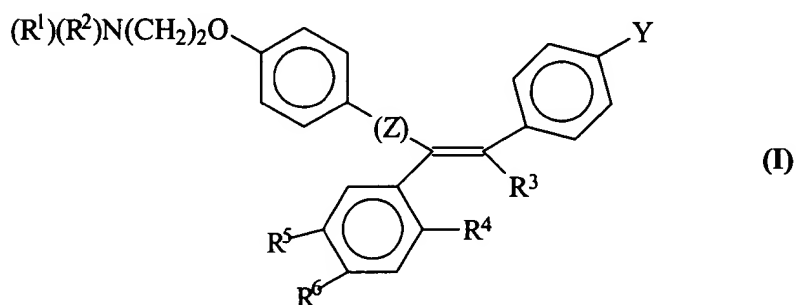
183. (New) The method of claim 182 wherein the increase in TGF-beta reduces or inhibits diabetic retinopathy.
184. (New) The method of claim 182 wherein the mammal is diabetic.
185. (New) The method of claim 184 wherein the diabetic has retinopathy.
186. (New) The method of claim 182 wherein the compound indirectly or directly increases the level of active TGF-beta in vascular tissue.
187. (New) The method of claim 182 wherein the compound is a TGF-beta production stimulator.

188. (New) The method of claim 182 wherein the compound is a TGF-beta activator.
189. (New) The method of claim 182 wherein the compound increases the production of TGF-beta mRNA.
190. (New) The method of claim 182 wherein the compound increases the cleavage of the latent form of TGF-beta.
191. (New) The method of claim 182 wherein the compound increases the bioavailability of TGF-beta.
192. (New) The method of claim 182 wherein the compound is idoxifene or a pharmaceutically acceptable salt thereof.
193. (New) The method of claim 182 wherein the compound is toremifene or a pharmaceutically acceptable salt thereof.
194. (New) The method of claim 182 wherein the compound is droloxifene or a pharmaceutically acceptable salt thereof.
195. (New) The method of claim 182 wherein the compound is tamoxifen or a pharmaceutically acceptable salt thereof.
196. (New) The method of claim 158, 173 or 182 wherein the compound forms cellular DNA adducts at level which is reduced relative to DNA adduct formation by tamoxifen.
197. (New) The method of claim 158, 173 or 182 wherein the compound has estrogenic activity which is reduced relative to the estrogenic activity of

tamoxifen.

198. (New) The method of claim 158, 173 or 182 wherein the compound does not form cellular DNA adducts.
199. (New) The method of claim 158, 173 or 182 wherein the compound has no estrogenic activity.
200. (New) A method of increasing the level of TGF-beta in a mammal in need thereof, comprising administering an effective amount of an agent that directly or indirectly elevates the level of active TGF-beta in said mammal, wherein the agent has reduced estrogenic activity relative to tamoxifen, reduced DNA adduct formation relative to tamoxifen, or any combination thereof.
201. (New) The method of claim 200 wherein the agent is a structural analog of tamoxifen or a pharmaceutically acceptable salt thereof.
202. (New) The method of claim 200 wherein the agent is idoxifene or a pharmaceutically acceptable salt thereof.
203. (New) The method of claim 200 wherein the agent is toremifene or a pharmaceutically acceptable salt thereof.
204. (New) The method of claim 158 wherein the non-aortal smooth muscle cells which are inhibited are present in a non-coronary artery.
205. (New) The method of claim 158, 173, 182, or 200 wherein the administration increases the level of latent TGF-beta relative to the level of latent TGF-beta prior to said administration.

206. (New) The method of claim 158, 173, 182, or 200 wherein the administration increases the level of active TGF-beta relative to the level of active TGF-beta prior to said administration.
207. (New) A therapeutic method for preventing or treating a vascular indication characterized by a decreased lumen diameter comprising administering to a mammal at risk of or afflicted with said vascular indication, a cytostatic dose of a therapeutic agent, wherein the therapeutic agent is a compound of formula (I):

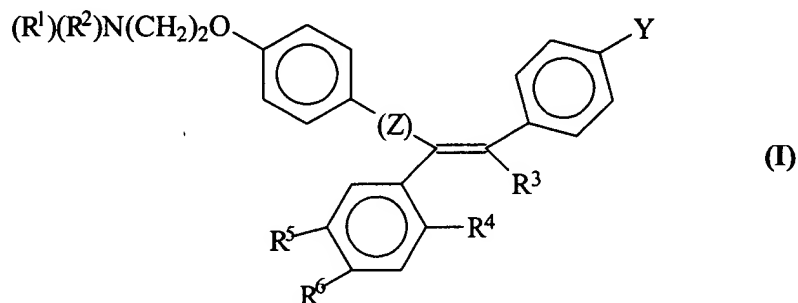


wherein Z is C=O or a covalent bond; Y is H or O(C₁-C₄)alkyl, R¹ and R² are individually (C₁-C₄)alkyl or together with N are a saturated heterocyclic group, R³ is ethyl or chloroethyl, R⁴ is H or together with R³ is -CH₂-CH₂- or -S-, R⁵ is I, OH, O(C₁-C₄)alkyl or H and R⁶ is I, O(C₁-C₄)alkyl or H with the proviso that when R⁴, R⁵ and R⁶ are H, R³ is not ethyl; or a pharmaceutically acceptable salt thereof.

208. (New) The method of claim 207 wherein the cytostatic dose is effective to increase the level of TGF-beta so as to decrease lesion formation or

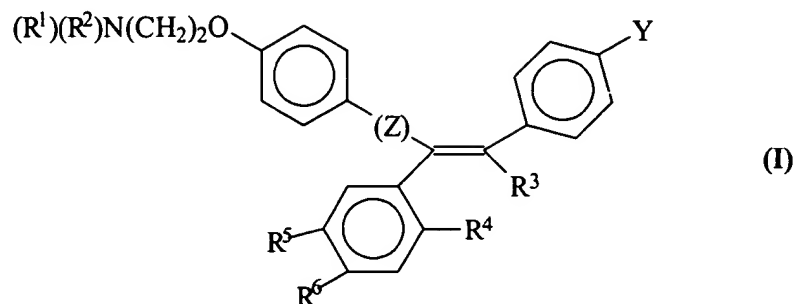
development, inhibit lipid accumulation, increase plaque stability, maintain or increase vessel lumen diameter, or any combination thereof.

209. (New) The method of claim 207 wherein the compound of formula (I) is idoxifene, 4-iodotamoxifen, 3-iodotamoxifen, toremifene, or a pharmaceutically acceptable salt thereof.
210. (New) The method of claim 207 wherein the administration is systemic.
211. (New) The method of claim 207 wherein the compound of formula (I) is administered in a sustained release dosage form.
212. (New) An intravascular stent comprising a cytostatic amount of a compound of formula (I):



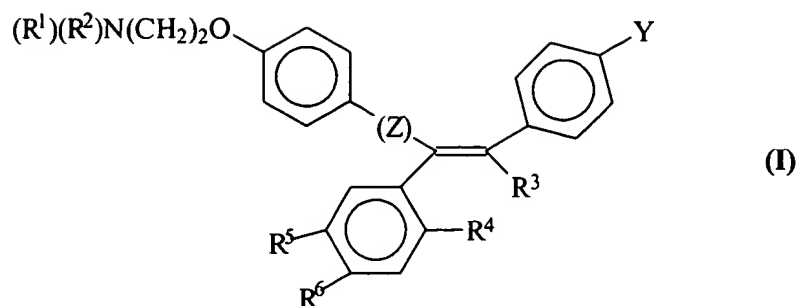
wherein Z is C=O or a covalent bond; Y is H or O(C₁-C₄)alkyl, R¹ and R² are individually (C₁-C₄)alkyl, R³ is ethyl or chloroethyl, R⁴ is H or together with R³ is -CH₂-CH₂- or -S-, R⁵ is I, OH, O(C₁-C₄)alkyl or H and R⁶ is I, O(C₁-C₄)alkyl or H; or a pharmaceutically acceptable salt thereof; effective to inhibit stenosis or reduce restenosis of a mammalian vessel following placement of the stent in said vessel.

213. (New) An intravascular stent comprising a cytostatic amount of a compound of formula (I):



wherein Z is C=O or a covalent bond; Y is H or O(C₁-C₄)alkyl, R¹ and R² are individually (C₁-C₄)alkyl, or together with N are a saturated heterocyclic group, R³ is ethyl or chloroethyl, R⁴ is H or together with R³ is -CH₂-CH₂-, R⁵ is I, OH, O(C₁-C₄)alkyl or H and R⁶ is I, O(C₁-C₄)alkyl or H; or a pharmaceutically acceptable salt thereof; effective to inhibit stenosis or reduce restenosis of a mammalian vessel following placement of the stent in said vessel.

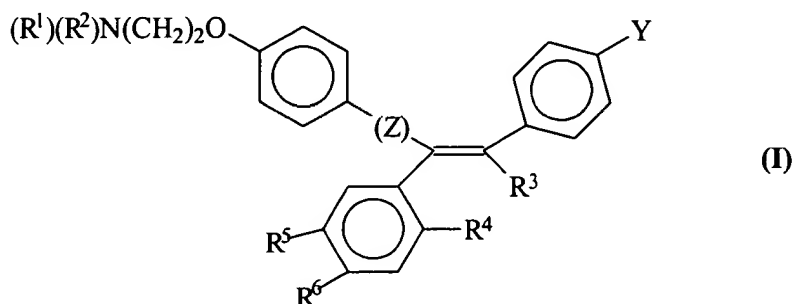
214. (New) The stent of claim 212 or 213, wherein R³ is not ethyl when R⁴, R⁵ and R⁶ are H.
215. (New) An intravascular stent comprising a cytostatic amount of a compound of formula (I):



wherein Z is C=O or a covalent bond; Y is H or O(C₁-C₄)alkyl, R¹ and R² are individually (C₁-C₄)alkyl or together with N are a saturated heterocyclic group, R³ is ethyl or chloroethyl, R⁴ is H or together with R³ is -CH₂-CH₂- or -S-, R⁵ is I, OH or O(C₁-C₄)alkyl and R⁶ is I, O(C₁-C₄)alkyl or H; or a pharmaceutically acceptable salt thereof; effective to inhibit stenosis or reduce restenosis of a mammalian vessel following placement of the stent in said vessel.

216. (New) The intravascular stent of claim 212, 213 or 215 that is adapted to maintain expanded vessel luminal area following angioplasty.
217. (New) The intravascular stent of claim 216 wherein the compound of formula (I) is in a sustained release dosage form.
218. (New) The intravascular stent of claim 216 wherein the matrix of the stent comprises the compound of formula (I).
219. (New) The intravascular stent of claim 212, 213 or 215 wherein the stent comprises a coating comprising the compound of formula (I).

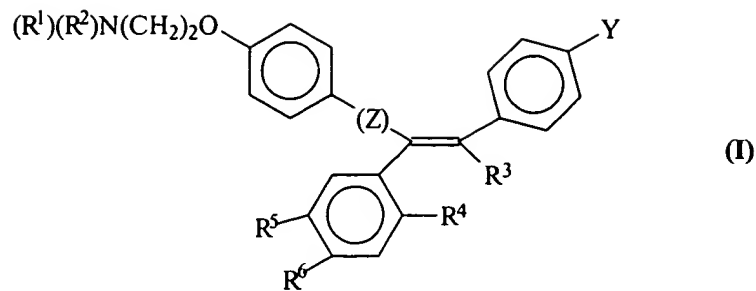
220. (New) The intravascular stent of claim 219 wherein the coating is biodegradable.
221. (New) The intravascular stent of claim 219 wherein the coating is porous or permeable to the inhibitor.
222. (New) The therapeutic stent of claim 212, 213 or 215 wherein the matrix of the stent is formed from a porous or permeable non-biodegradable material.
223. (New) The therapeutic stent of claim 212, 213 or 215 in which the intravascular stent comprises metal or plastic.
224. (New) The therapeutic stent of claim 212, 213 or 215 wherein the matrix is formed from a biodegradable material.
225. (New) A therapeutic method comprising inhibiting vascular smooth muscle cell proliferation comprising administering to a mammal an effective cytostatic antiproliferative amount of a compound of formula (I):



wherein Z is C=O or a covalent bond; Y is H or O(C₁-C₄)alkyl, R¹ and R² are individually (C₁-C₄)alkyl or together with N are a saturated heterocyclic

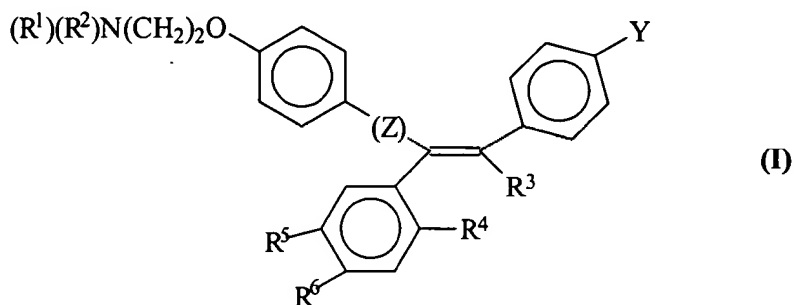
group, R³ is ethyl or chloroethyl, R⁴ is H or together with R³ is -CH₂-CH₂- or -S-, R⁵ is I, OH, O(C₁-C₄)alkyl or H and R⁶ is I, O(C₁-C₄)alkyl or H; or a pharmaceutically acceptable salt thereof, wherein the administration is by placement of a vascular shunt or intravascular stent comprising said compound.

226. (New) The method of claim 225 wherein the compound is droloxifene, raloxifene, toremefine, tamoxifen, idoxifene, or a pharmaceutically acceptable salt thereof.
227. (New) The method of claim 225 wherein the shunt or stent matrix is impregnated with the compound of formula (I).
228. (New) The method of claim 227 wherein the shunt or stent comprises a coating incorporating said compound of formula (I).
229. (New) The method of claim 225 wherein the shunt or stent comprises a coating incorporating said compound of formula (I).
230. (New) The method of claim 227, 228, or 229 wherein said matrix or said coating is biodegradable.
231. (New) A therapeutic method for treating a condition selected from the group consisting of arteriosclerosis and small vessel disease, comprising administering to a mammal afflicted with said condition, an effective amount of a compound of formula (I):



wherein Z is C=O or a covalent bond; Y is H or O(C₁-C₄)alkyl, R¹ and R² are individually (C₁-C₄)alkyl or together with N are a saturated heterocyclic group, R³ is ethyl or chloroethyl, R⁴ is H, R⁵ is I, O(C₁-C₄)alkyl or H and R⁶ is I, O(C₁-C₄)alkyl or H with the proviso that when R⁴, R⁵, and R⁶ are H, R³ is not ethyl; or a pharmaceutically acceptable salt thereof.

232. (New) A method of treating diabetic retinopathy by increasing the level of TGF-beta in a mammal in need thereof, comprising administering an effective amount of a compound of formula (I):



wherein Z is C=O or a covalent bond; Y is H or O(C₁-C₄)alkyl, R¹ and R² are individually (C₁-C₄)alkyl or together with N are a saturated heterocyclic

group, R^3 is ethyl or chloroethyl, R^4 is H or together with R^3 is $-\text{CH}_2-\text{CH}_2-$ or $-\text{S}-$, R^5 is I, OH, $\text{O}(\text{C}_1-\text{C}_4)\text{alkyl}$ or H and R^6 is I, $\text{O}(\text{C}_1-\text{C}_4)\text{alkyl}$ or H with the proviso that when R^4 , R^5 , and R^6 are H, R^3 is not ethyl; or a pharmaceutically acceptable salt thereof.